## REMARKS

This is in response to the Office Action dated 05/27/2008.

Claims 29-37 are currently pending.

**Claims 29-36 were rejected under 35 USC § 103(a) as being unpatentable over Tzou et al. (5,776,433) in view of Saidi et al. (6,241,969).**

Applicants respectfully traverse.

The Office Action refers (p. 4, last paragraph) to "the general teachings of Tzou et al. on solution formulations containing active agents such as flunisolide . . . ." However, there is no such "general teaching" in Tzou et al. Tzou et al. discloses that a solution formulation of flunisolide has improved chemical stability in a glass or resin coated aluminum canister. Tzou et al. is silent as to other steroids.

The present inventors discovered specifically why some steroids degrade in solution and some do not, and how to improve stability of the unstable ones.

It is worth noting that prior art such as US 5,776,432 discloses that HFA formulations of the steroid beclomethasone dipropionate (BDP)[1] are chemically stable in conventional aluminum canisters, but that presence of common surfactants such as oleic acid reduces chemical stability. In other words, the prior art regarding BDP steroid solutions would tend to teach away from the present invention because it discloses stable solutions in conventional aluminum containers and focuses on surfactant as the source of stability problems.

Saidi et al. discloses that aqueous nebulizer solutions of many steroids, some which have a C-21 OH group and some which do not, are chemically stable (col. 10, line 36). Saidi et al. even suggests *flunisolide* (in the laundry list at col. 6, lines 14-30) is chemically stable, at least in aqueous nebulizer solutions. Saidi et al. thus effectively teaches away from there being a chemical stability problem (at least for aqueous nebulizer products in glass vials).

When the problem itself is not known or obvious from the cited references, the claimed solution to the problem (i.e., using coated metal containers) also would not have been obvious. Tzou et al. is limited to flunisolide and Saidi et al. suggests there is no problem.

Moreover, Saidi et al. cannot be combined with Tzou et al. because the result would be inoperable. Saidi et al. requires an aqueous formulation of at least 70% water (see claim 1). Large amounts of water, because water is not a propellant, would disable an HFA formulation so it would no longer function as an aerosol.

Withdrawal of the obviousness rejection based on Tzou et al. in view of Saidi et al. is therefore requested.

**Claim 37 was rejected under 35 USC § 103(a) as being unpatentable over Tzou et al. (5,776,433) in view of Saidi et al. (6,241,969) in further view of Randall (3,923,484).**

Applicants respectfully traverse. Neither Tzou et al., Saidi et al. nor Randall disclose or suggest putting a glass coating on the interior of a medicinal aerosol canister. Randall discloses a method of making fused silica glass bodies, but not glass coatings on metal. The combination with Randall thus does not arrive at the present claims.

Accordingly, claim 37 would not have been obvious and withdrawal of the rejection is therefore requested.

**Claims 29-31 and 34-36 were rejected under 35 USC § 103(a) as being unpatentable over Porush et al. (2,868,691) in view of Ashurst et al. (6,143,277).**

Applicants respectfully traverse.

Ashurst et al. deals with micronized drug suspension formulations (see, e.g., col. 5, lines 30-35) and thus implicitly teaches *away* from the present invention. The purpose of the coating in Ashurst et al. is to prevent drug from adhering to the can walls (col. 1, lines 59-63). One skilled in the art would have no reason based on Ashurst et al. to make any solution formulation in a coated canister.

The present inventors discovered why certain particular steroids have poor chemical stability when in HFA solution formulations in conventional aluminum canisters, and that such problem could be solved by using an inert coating. Neither Porush et al. nor Ashurst et al. have

[1] To avoid misunderstanding, please note that beclomethasone dipropionate does not have an OH group at the C-17 or C-21 position, whereas beclomethasone and beclomethasone monopropionate, listed in the present application, do.

any teaching of either the problem or its solution, and the asserted combination actually requires ignoring that Ashurst et al. is expressly concerning particulate suspensions.

Withdrawal of the rejection is therefore request.

**Claims 32-33 were rejected under 35 USC § 103(a) as being unpatentable over Porush et al. (2,868,691) in view of Ashurst et al. (6,143,277) and further in view of Ercoli et al. (3,755,302).**

Applicants respectfully traverse.

In addition to the reasons set forth above in connection with Porush et al. and Ashurst et al., Ercoli et al. merely adds that dexamethasone and betamethasone 17-valerate were known steroids. It would not, however, have been obvious that such steroids would be chemically unstable in aluminum canisters or that such instability could be alleviated by using coated canisters.

As noted above, the present inventors discovered why some steroids are unstable and others are not, and how to improve stability of the unstable ones. Neither Porush et al., Ashurst et al., nor Ercoli et al. provide any guidance in this regard.

Withdrawal of the rejection is therefore requested.

**Claims 29-36 were rejected under 35 USC § 103(a) as being unpatentable over Blondino et al. (6,290,930) in view of Ashurst et al. (6,143,277) and in view of Ercoli et al. (3,755,302).**

Applicants respectfully traverse.

While Blondino et al. discloses a solution formulation of budesonide (a C-21 OH steroid) in HFA propellant, there is no recognition whatsoever of a chemical stability problem or how to solve it. To the contrary, Blondino et al. appears to teach that the formulations are stable in a plastic coated glass bottle[2] or an aluminum canister.

Again, as noted above, the present inventors (i) discovered that, while many steroids are stable, a certain type of steroid having a C-21 OH group undergoes chemical degradation in HFA solution formulations, (ii) that such chemical degradation is caused in significant part by contact

with metal oxides from the container, and (iii) that using an inert coating greatly reduces the chemical degradation problem.

While Ashurst et al. discloses coated canisters for purposes of preventing particulate drug suspensions from adhering to the walls, it teaches nothing about the chemical instability of C-21 OH steroids in solution or how to solve such problem. There would have been no reason or motivation to use the coated canisters of Ashurst et al. in the solution formulation of Blondino et al.

Ercoli et al. discloses various steroids, but nothing relevant to MDI solutions in HFA propellant.

The Office Action observes that all of the elements of the claims can be found in the prior art. However, while perhaps true in a general sense, that is not the proper test of patentability because there is no basis for selecting the specific elements out of context and combining them to arrive at the present claims. There must be some reasonable basis for one skilled in the art to arrive at the claimed invention from the prior art.

**Claims 29-31 and 34-36 were rejected under 35 USC § 103(a) as being unpatentable over Ashurst et al. (6,131,566) and in view of Saidi et al. (6,241,969).**

As already noted above, Ashurst et al. deals with micronized drug suspension formulations (see, e.g., col. 5, lines 29-34) and thus implicitly teaches *away* from the present invention. The purpose of the coating in Ashurst et al. is to prevent drug from adhering to the can walls (col. 1, lines 59-63). One skilled in the art would have no reason based on Ashurst et al. to make any solution formulation in a coated canister.

Saidi et al. discloses that aqueous nebulizer solutions of many steroids, some which have a C-21 OH group and some which do not, are chemically stable (col. 10, line 36). Saidi et al. even suggests *flunisolide* (in the laundry list at col. 6, lines 14-30) is chemically stable, at least in aqueous nebulizer solutions. Saidi et al. thus effectively teaches away from there being a chemical stability problem (at least for aqueous nebulizer products in glass vials).

Moreover, Saidi et al. cannot be combined with Ashurst et al. because the result would be inoperable. Saidi et al. requires an aqueous formulation of at least 70% water (see claim 1).

[2] Conventional glass MDI aerosol containers have an exterior plastic coating for safety purposes.

Large amounts of water, because water is not a propellant, would disable an HFA formulation so it would no longer function as an aerosol.

Withdrawal of the obviousness rejection based on Ashurst et al. in view of Saidi et al. is therefore requested.

**Claim 37 was rejected under 35 USC § 103(a) as being unpatentable over Ashurst et al. (5,776,433) in view of Saidi et al. (6,241,969) in further view of Randall (3,923,484).**

Applicants respectfully traverse. Neither Ashurst et al., Saidi et al. nor Randall disclose or suggest putting a glass coating on the interior of a medicinal aerosol canister. Randall discloses a method of making fused silica glass bodies, but not glass coatings on metal. The combination with Randall thus does not arrive at the present claims.

Accordingly, claim 37 would not have been obvious and withdrawal of the rejection is therefore requested.

**Claim 29-36 were rejected based on obviousness-type double patenting over claims 1-3 and 6-17 of U.S. Patent 6,610,273 in view of Tzou et al. (5,776,433).**

Enclosed herewith is a terminal disclaimer which is deemed to obviate the rejection. Applicants wish to note that in addition to US6,610,273 (Wu et al.), a terminal disclaimer is also submitted for US6,315,985 (Wu et al.).

**Claim 29-37 were rejected based on provisional obviousness-type double patenting over claims 29-37 of co-pending application 11/061,529 (US 20050220717).**

It is believed that a terminal disclaimer was previously submitted with Applicants' submission of March 18, 2008. If none was received, Applicants request to hold this issue in abeyance until one of the two applications are patented.

In view of the above, it is submitted that the application is in condition for allowance. Examination and reconsideration of the application.

Respectfully submitted,

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